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Extended Lymphadenectomy in Patients With Pancreatic Cancer Is Debatable

Gregory Sergeant · Emmanuel Melloul · Mickael Lesurtel · Michelle L. DeOliveira · Pierre-Alain Clavien

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Abstract Lymph node staging is one of the most important factors in determining the prognosis after resection of pancreatic ductal adenocarcinoma. Despite ongoing efforts to further refine lymph node staging, the debate on the extent of lymphadenectomy during pancreaticoduodenectomy is still open. The purpose of this review was to summarize the evidence about performing standard lymphadenectomy during curative resection of pancreatic cancer. All four prospective randomized controlled trials published concluded that extended lymphadenectomy does not contribute to better oncologic outcome for patients with adenocarcinoma of the pancreatic head. Indeed, one major drawback of extended lymphadenectomy is the higher risk of persistent postoperative diarrhea. No prospective randomized studies could be found on the role of extended lymphadenectomy in patients with adenocarcinoma of the corpus and tail. Based on current evidence there is no indication that extended lymphadenectomy should be performed routinely during resection of pancreatic cancer.

Introduction

Despite continuous efforts to improve survival of patients with pancreatic cancer, little progress has been achieved over the past three decades, mainly because most patients with pancreatic adenocarcinoma present at an advanced stage. Although curative surgery is an option in fewer than 30 % of cases, it remains the only treatment that offers a chance for long-term survival. The reported 5-year survival rates after curative resection still range between 10 and 20 % [1].

Significant improvements in preoperative and postoperative tumor staging have considerably improved our capability to estimate long-term prognosis reliably and to select patients who may benefit the most from neoadjuvant treatment. Lymph node metastasis is one of the most relevant prognostic factors in pancreatic cancer [2]. It is part of the TNM staging system [3], although its use in selecting patients for adjuvant treatment and prognostic value has remained controversial. Studies have shown that lymph node status can be further refined by calculating the total number of harvested lymph nodes, providing information on a minimum of 15 lymph nodes [4], the total number of positive lymph nodes [5], the lymph node ratio (LNR) [6–10], extracapsular lymph node involvement [11], direct invasion of lymph nodes versus true lymph node metastasis [12], and micrometastatic involvement [13].

Whether to perform an extended lymphadenectomy during pancreatic resection for adenocarcinoma of the pancreas is not a new debate. In fact, leading Japanese surgeons had already adopted extended lymphadenectomy during the mid-1970s after the concept of regional pancreatectomy had been introduced by Fortner [14]. These surgeons justified their new concept of radical lymphadenectomy during pancreatic surgery on the basis of other oncologic resections, such as D3 lymphadenectomy for gastric cancer [15]. The use of extended lymphadenectomy for pancreatic cancer, however, failed to gain acceptance in the Western countries.

Emmanuel Melloul contributed equally as first author. Michelle L. DeOliveira and Pierre-Alain Clavien contributed equally as senior author.

G. Sergeant · E. Melloul · M. Lesurtel · M. L. DeOliveira · P.-A. Clavien (✉)
Department of Surgery, Swiss HPB and Transplant Center, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland
e-mail: clavien@access.uzh.ch

Evidence

Trials

Most studies suggesting an advantage for extended lymphadenectomy are nonrandomized retrospective studies and should therefore be interpreted with caution. A recent review by Pavlidis et al. [16] summarized the level-A evidence of four randomized controlled trials on extended versus standard lymphadenectomy. They arrived at the conclusion that extended lymphadenectomy does not offer any benefit in terms of long-term survival.

The first randomized control trial (RCT) was a multicenter Italian study that randomly assigned 40 patients to standard pancreatoduodenectomy (PD) and 41 patients to PD with additional extended lymphadenectomy [17]. As expected, a significant difference in retrieved lymph nodes was found between standard and extended PD with, respectively a mean of 13 versus 20 harvested lymph nodes. Mortality and morbidity rates between the two groups were comparable. Of note, on subgroup analysis of patients with positive lymph nodes only, overall survival was significantly longer for the group of patients treated by PD with extended lymphadenectomy.

The largest RCT to date was performed at Johns Hopkins. They randomly assigned 146 patients to undergo standard PD and 148 patients to undergo PD with extended lymphadenectomy, associated with distal gastrectomy in about one-third of the cases [18, 19]. The Johns Hopkins trial, however, also included patients with periampullary carcinoma, distal cholangiocarcinoma, and duodenal carcinoma. These entities have different 5-year survivals and slightly different patterns of lymph node metastasis. The study found no evidence of extended lymphadenectomy superiority.

More recently, an RCT from the Mayo Clinic assigned 40 patients to standard PD and 39 patients to PD with extended lymphadenectomy [20]. Similarly, this study failed to show a significant difference in overall survival between patients undergoing PD with standard versus extended lymphadenectomy. The Mayo Clinic trial also performed a subgroup analysis on patients with lymph node metastasis. In contrast to the RCT by Pedrazzoli et al. [17], no survival difference was found between the two groups. This difference might be explained by the fact that all patients in the Mayo Clinic trial underwent adjuvant chemoradiation following PD.

The most recent multicenter RCT from Japan, by Nimura et al. [21], randomly assigned 112 patients to either extended or standard lymphadenectomy during PD for pancreatic cancer of the head of the pancreas only. Interestingly, in this Japanese trial, none of the patients received adjuvant chemotherapy—in contrast to a variety of adjuvant regimens given to patients in the three previously conducted RCTs. These authors, similarly, failed to identify a benefit of extended lymphadenectomy in terms of overall survival. The extent of PD and lymphadenectomy for both the standard and extended group in the RCTs is illustrated in Table 1.

All RCTs (except for the Johns Hopkins trial) have been criticized because of low sample size and hence being underpowered, leading to a type 2 error. A small difference in survival difference is also unlikely to be picked up in the absence of a standardized postoperative treatment. Finally, the 20 % 2-year overall survival after standard lymphadenectomy that was used to calculate the sample size in the Japanese trial is lower than expected [21]. A major concern raised by the analysis of the available RCTs along with the retrospective studies is the increased morbidity associated with extended lymphadenectomy [22]. In light of similar overall survival, secondary outcome variables (e.g., severe complications, operating time, hospital stay, quality of life) should be given more importance. Indeed, circular dissection of the celiac trunk and superior mesenteric artery may cause severe diarrhea because of injury of the periarterial neural plexus. This type of diarrhea is notably therapy-resistant and can severely impair the postoperative quality of life. Also, the extended lymphadenectomy results in a significant increase in operating time [23]. These drawbacks may result in significant additional cost (e.g., due to longer hospitalization times), which are not justified in view of the absence of any obvious benefit.

Thus, the current evidence does not support performing extended lymphadenectomy during PD for the treatment of pancreatic cancer. Interestingly, for adenocarcinoma of the body and tail of the pancreas requiring distal pancreatectomy (DP) with en bloc splenectomy, the optimal extent of lymphadenectomy is less clear, as no RCT is available to support either strategy. Also, in a recent series of 85 patients with carcinoma of the body and tail of the pancreas, no correlation was found between the anatomic locations of metastatic lymph nodes and survival [24]. Their results suggested that with this type of cancer nodal staging could be more informative if classified based on the number of metastatic lymph nodes and the LNR rather than anatomic location. However, the number of metastatic lymph nodes and the LNR are influenced by the extent of the resection. Therefore, although not associated with improved survival, sufficiently thorough lymph node sampling remains necessary to stage these patients correctly.

Lack of a true standard for lymphadenectomy during pancreatic cancer surgery

The lack of a true standard for lymphadenectomy during PD has complicated the interpretation of both retrospective

Table 1 Study characteristics of the four randomized clinical trials comparing standard versus extended lymphadenectomy during pancreaticoduodenectomy

	Pedrazzoli [17] (1998)		Yeo [18, 19] (1999 and 2002)		Farnell [20] (2005)		Nimura [21] (2012)	
	Multi-center		Single center		Single center		Multi-center	
	Standard	Extended	Standard	Extended	Standard	Extended	Standard	Extended
No. of patients	40	41	146	148	40	39	51	50
Resection type	PP or DG		PP	30 % DG	DG		PP, SP, DG	
Node dissection	En bloc		Sequential		Sequential		En bloc	
LN stations removed	LN5, 6, 8, 12, 13, 17	LN5, 6, 7, 8, 9, 11, 12, 13, 17	LN12[a], 13, 14, 17	LN3, 4, 5, 6, 8, 9, 11, 12, 13, 14, 15, 16, 17	LN3, 4, 6, 8a, 12[b], 13, 14[b], 17	LN3, 4, 6, 8(a, p), 12, 13, 14, 16, 17	LN13, 17	LN6, 8, 9, 12(a, b, p), 13, 14, 16
Operating time (min)	372	396	354	384	378	450	426	547
No. of LNs removed	13.3 (1–35)*	19.8 (3–76)*	17*	28.5*	15 (3–13)*	36 (6–74)*	13.3 (4–30)*	40.1 (15–81)*
N+ status	24 (60 %)	24 (59 %)	(82 %)	(77 %)	(55 %)	(68 %)	32 (63 %)	30 (60 %)
R0 resection	29 (72.5 %)	32 (78 %)	(80 %)*	(95 %)*	(76 %)	(82 %)	48 (94 %)	45 (90 %)
Adjuvant treatment (no.)	IORT (10)	IORT (9)	CRT (81)	CRT (83)	CRT	CRT	None	None
Mortality rate	2 (5 %)	2 (5 %)	6 (4 %)	3 (2 %)	0	1 (3 %)	0	1 (2 %)
1-, 3-, 5-Year survivals (%)	–	–	80/44/23 (75/34/13 %)	77/44/29 (73/38/29 %)	82/41/16	71/25/17	78/28/16	54/18/6
Median survival (months)	11.2	16.7	30.0	28.0	26.0	18.8	19.9	13.8

PP pylorus-preserving, *DG* distal gastrectomy, *SP* suprapyloric gastric transection, *LN* lymph node, *IORT* intraoperative radiation therapy, *CRT* chemoradiotherapy

* Significant differences between the two groups

[a] Nodes in the lower hepatoduodenal ligament

[b] Nodes in the right hepatoduodenal ligament for LN12, on the superior mesenteric artery for LN14

and prospective studies. When looking at the RCTs alone, all four trials obviously differed regarding the extent of their standard and extended lymphadenectomies [17, 19–21]. For instance, although resection of anterior and posterior pancreaticoduodenal lymph nodes (LN17, LN13), including infrapyloric nodes (LN6) and hepatoduodenal lymph nodes (LN12), is fairly standardized, resection of lymph nodes surrounding the common hepatic artery (LN8) is not. This lack of a true standard makes comparison among studies problematic. Interestingly, the recently proposed LNR [i.e., the ratio of involved nodes to the total number of examined lymph nodes (ELNs)] has been shown to be an independent prognostic factor after pancreatectomy for pancreatic adenocarcinoma. The LNR strongly correlates with outcome provided a certain number of lymph nodes are evaluated, suggesting that the prognostic accuracy of any lymph node variable depends on the total number of ELNs [25]. It is likely that the observed relative benefit of more-extensive lymphadenectomy may lie in a better prognostic evaluation, rather than any real therapeutic effect [26]. Whether more-extensive lymphadenectomy is beneficial to the patient remains unknown when fewer than a minimum number of lymph nodes (i.e., LN >15) are harvested [23].

Pattern of recurrence after PD for pancreatic cancer

The pattern of recurrence after PD for pancreatic cancer has only scarcely been studied. In a recent single-center study of 145 patients undergoing pancreatic resection for pancreatic adenocarcinoma, 110 patients developed recurrence during follow-up. Locoregional recurrence was documented in 44 (40 %) of the patients. Of note, isolated locoregional recurrence was relatively uncommon (17 %), and liver metastasis was observed in 57 of 110 (52 %) patients [27]. It is unlikely that extending the degree of lymphadenectomy would substantially decrease the number of locoregional recurrences as the majority of them can be at least partially attributed to R1 resections. Nevertheless, among N1 patients, a higher number of positive lymph nodes and an LNR >0.4 were associated with the highest rate of local failure following PD and adjuvant 5-fluorouracil-based chemoradiation therapy [28].

Patterns of lymph node metastasis and recurrence

Aside from the lack of evidence to support extended lymphadenectomy based on the RCTs and prospective cohort studies, some evidence against extended lymphadenectomy may come from the analysis of the distribution pattern of lymph node metastases of pancreatic cancer. During the 1970s, Cubilla et al. [29] studied the pattern of lymph node involvement in cancer of the head of the pancreas. One-third of 22 extended lymphadenectomies examined were found to have nodal metastases along the superior and inferior borders of the corpus of the pancreas. Until the detailed Japanese landmark studies by Kayahara et al. [30] and Ishikawa et al. [31], the relative anatomic distributions of lymph node metastases in pancreatic cancer were unknown. The lymph node stations most commonly involved are the posterior pancreaticoduodenal lymph nodes (51 and 49 %, respectively), the superior mesenteric artery lymph nodes (37 and 47 %, respectively), and the inferior pancreaticoduodenal lymph nodes (33 and 37 %, respectively). The paraaortic lymph nodes were involved in up to 16 % patients. These data were confirmed in the Japanese RCT [21]. Of note, these studies showed that lymph node stations typically falling outside a standard lymphadenectomy were the sole sites of lymph node metastases in only 5 % of the cases. The prediction of distant lymph node metastasis could be helpful not only for selecting patients for a more extended lymphadenectomy but also for the use of neoadjuvant therapy. Regarding the use of extended lymphadenectomy, it is important to remember that lymph node metastases around the superior mesenteric artery or any of the other less frequently involved lymph nodal stations (e.g., splenic artery) are associated with a poorer prognosis, and such dismal outcome cannot yet be reversed with a more-extended lymphadenectomy. Unlike other tumors such as gastric cancer, extensive lymph node involvement with pancreatic cancer should be considered a marker of aggressive tumor biology and rapid progression. Therefore, lymphadenectomy only partially contributes to the therapeutic success. Neoadjuvant therapy may have greater potential when selectively administered to patients with a high incidence of distant paraaortic (LN16) lymph node metastasis, which corresponds to those with T3 or higher stage tumors, with arterial and perineural invasion [32].

It is important to stress that those interaortocaval lymph nodes (right paraaortic lymph nodes—LN16) for pancreatic cancer of the head and celiac trunk lymph nodes (LN9) for tumors of the body and tail of the pancreas are classified as M1 disease according to the TNM classification [3]. Indeed, paraaortic M1 lymph node spread indicates a poor prognosis with median survival rates of approximately 6 months. Paraaortic lymph nodes may be involved in up to 30 % of patients undergoing PD, and rejecting those patients for curative resection would probably result in a better approach.

Another argument against extended lymphadenectomy is that pancreatic adenocarcinoma does not exclusively metastasize via the lymphatic system. Transperitoneal and subperitoneal spread, including perineural invasion and periarterial invasion, provide a direct route from the pancreas to the peritoneal cavity and retroperitoneum.

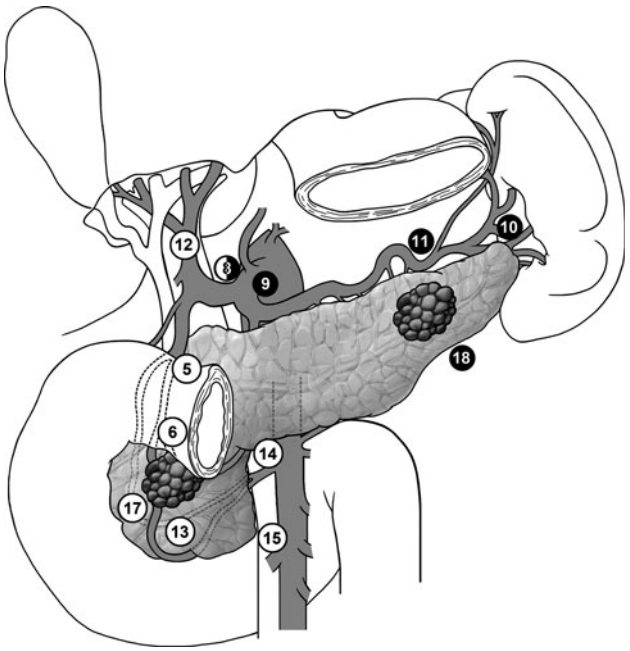

Fig. 1 Standard lymphadenectomy during pancreatectomy for pancreatic adenocarcinoma of the head and corpus or tail of the pancreas. The lymph node stations (according to the Japanese classification [15]) resected during pancreaticoduodenectomy are *white with black numbers*. Lymph node stations resected during en bloc left pancreatectomy with splenectomy are *black with white numbers*. Lymph nodes around the common hepatic artery (LN8) were resected during both procedures

Moreover, hematogenous metastatic routes contribute to distant spread of the disease. Indeed, both lymphatic and vascular invasion may lead to the venous circulation of tumor cells. In addition, it has been suggested that extensive lymph node invasion with extracapsular lymph node involvement resulting in shunting of tumor cells to the vascular system drives these alternative routes [11].

In light of the availability of more effective adjuvant therapies, the potential benefit of extended lymphadenectomy may further shrink. Indeed, about two-thirds of patients do receive adjuvant therapies after pancreatic resection for pancreatic adenocarcinoma [33]. On multivariable analysis, major postoperative complications were associated with decreased utilization of adjuvant therapy. If postoperative morbidity is increased after extended lymphadenectomy, more patients will not be fit enough to be offered chemotherapy and thereby miss their benefits.

Standard lymphadenectomy—Zurich approach

Adenocarcinoma of the head of the pancreas

A standard lymphadenectomy is advisable for almost all pancreatic adenocarcinomas, as proposed by a recent expert consensus statement [23]. The extent of lymphadectomy is illustrated in Fig. 1 (white lymph node stations). During PD, interaortocaval lymph nodes (part of LN16) are sampled during the Kocher maneuver. Positive interaortocaval lymph nodes are classified as M1 disease according to the TNM classification, implying a median survival of no more than 7.8 months for patients with an extended lymphadenectomy [32]. Therefore, in most centers, the operation is aborted in older, higher-risk patients if this lymph node station is seen to be positive on frozen section. Palliative PD can be considered on a case-by-case basis. During dissection of the hepatoduodenal ligament, the lymph nodes surrounding the common hepatic artery (LN8) and both sides of the hepatoduodenal ligament (LN12) including the retroportal lymph nodes are dissected—if possible, en bloc with the specimen and distal bile duct. The infrapyloric (LN6) and suprapyloric (LN5) lymph nodes are kept with the resection specimen or sampled in case of partial gastrectomy or harvested if duodenal preservation is the choice. The gastroepiploic vein is ligated at its origin from the superior mesenteric or middle colic veins. The anterior (LN17) and posterior (LN13) lymph nodes around the superior and inferior pancreaticoduodenal veins are not dissected from the specimen and are routinely included with resection of the head of the pancreas. Particular care is taken to resect the complete uncinate process and lymph nodes right of the superior mesenteric artery (LN14). In selected cases with portal vein involvement, we advocate a superior mesenteric artery approach, as the first step.

Adenocarcinoma of the corpus or tail of the pancreas

En bloc splenectomy after early ligation of the splenic artery at its origin of the celiac trunk is performed for distal pancreatectomy. Radical antegrade modular pancreatosplenectomy (RAMPS) is an alternative approach when there is concern about the posterior resection margin [34]. The extent of lymphadenectomy is illustrated in Fig. 1 (black lymph node stations). All the lymph nodes along the splenic artery (LN11) up to the splenic hilum (LN10) are resected. Care is taken to remove lymph nodes at the superior and inferior (LN18) border of the pancreas when mobilizing the pancreatic tail and body up to the level of the junction of the splenic and portal vein. Lymph nodes at the celiac trunk (LN9) and common hepatic artery (LN8) are also sampled. Complete en bloc clearance of the lymph nodes around the celiac axis is generally avoided for two reasons: first to prevent morbidity arising from damage to the mesenteric nerve plexus; second, because these nodes are considered M1 in the TNM classification. When positive those nodes are associated with such a poor prognosis that resection is no longer justified.

Conclusions

There is currently no evidence for a benefit of extended lymphadenectomy during surgery for pancreatic adenocarcinoma. Other refinements of lymph node staging, such as the LNR and extra-capsular lymph node invasion may be stronger predictors of oncologic outcome. However, based on current scientific evidence, only standard lymphadenectomy should be performed routinely during resection of pancreatic cancer.

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